HEALTH ECONOMICS ANALYSIS PLAN (HEAP) for TRIUMPH

VERSION 1.0 (25/01/2021)

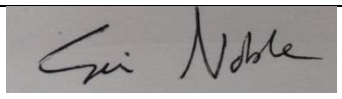
Contents

Section 1: HEAP Administrative Information

Title	Health Economic Analysis Plan (HEAP) for the TRIUMPH trial: a cluster randomised controlled trial to assess whether the use of non-pharmacological and non-surgical interventions improves lower urinary tract symptoms (LUTS) in men in primary healthcare
Trial registration number; registry	ISRCTN11669964 prospectively registered 12/04/2018; ISRCTN registry
Source of funding	National Institute for Health Research (NIHR), Health Technology Assessment Programme- Reference number 16/90/03
Purpose of HEAP	The purpose of the HEAP is to describe the analysis and reporting procedure intended for the economic analyses to be undertaken. The analysis plan is designed to ensure that there is no conflict with the protocol and associated statistical analysis plan (SAP), and it should be read in conjunction with them.
Trial protocol version; date	This document has been written based on information contained in the trial protocol version 6.0, dated 04/04/2019
Trial Statistical Analysis Plan (SAP) version, date	Version 1.0 (31/7/2020)
Trial HEAP version, date	1.0, 25/01/2021
HEAP revisions	n/a
Roles and responsibilities	The HEAP was prepared by Dr Madeleine Cochrane (Junior Health Economist) and approved by Dr Sian Noble (Senior Health Economist). The trial health economists (Dr Madeleine Cochrane and Dr Sian Noble) are responsible for conducting and reporting the economic evaluation in accordance with the HEAP

APPROVALS

The following people have reviewed the Health Economics Analysis Plan and are in agreement with the contents.

Role	Name	Signature	Date
Author	Dr Madeleine Cochrane		25/01/2021
Lead Health Economist	Dr Sian Noble		03/02/2021
Chief Investigator	Professor Marcus Drake		03/02/2021

Section 2: Trial Introduction & Background

2.1 Trial Background and Rationale

Lower-urinary tract symptoms (LUTS) in men, which can relate to storage or voiding, significantly impact on men's quality of life (1-3). The UK's National Institute for Health and Care Excellence (NICE) recommend that, after key assessments have been carried out, the initial treatment for LUTS should be conservative treatment (4). Assessing symptoms and offering conservative treatment is time-consuming and therefore challenging for GPs to fit within a single consultation. Consequently, conservative treatment may be ineffective in primary care, with men simply prescribed medication for their prostate, inappropriately referred to secondary care (5) or enduring persistent symptoms.

2.2 Aim of the Trial

To determine whether a care pathway including manualised and standardised application of non-pharmacological and non-surgical interventions is superior to usual care, in terms of symptom severity reported one year after consent.

2.3 Objectives of the trial

The primary objective will be measured using overall International Prostate Symptom Score (IPSS) reported 12 months after consent. The secondary objectives of the trial are to compare the differences between comparator groups for the following outcomes:

- Disease-specific quality of life (QoL)
- Symptomatic outcomes
- Relative harms
- Cost-effectiveness
- Use of NHS resources
- Health-related QoL (HRQoL) and general health
- Acceptability of assessment and care provided
- Patients' perceptions on their LUTS condition

2.4 Trial population

Thirty National Health Service (NHS) General Practice (GP) sites (comprising 32 GP practices) from the UK's West of England and Wessex Clinical Research Network (CRN) regions took part in the study. GP practices were eligible to take part in the trial if they had an adequate number of potentially eligible patients and treatment-room space for intervention delivery. Where possible, sites were selected to achieve a range in patient list size, deprivation score and preference on whether existing practice staff or a trial research nurse delivered the intervention. Males ≥18 years old, who considered themselves to have bothersome LUTS and who had presented to primary care with at least one symptom of LUTS within the last 5 years were invited to take part in the trial if they did not meet any of the exclusion criteria.

2.5 Intervention and comparators

TRIUMPH is a conservative intervention for treating LUTS, involving the provision of a standardised booklet with information and active management advice for men in primary care presenting with LUTS. The intervention includes a manualised care component where participants receive consultations from one of four healthcare professionals (HCPs): GP practice clinical nurse, GP research nurse, healthcare assistant or dedicated trial research nurse. All HCPs received training on intervention delivery and are invited to attend ongoing HCP teleconferences to support the initial training.

The HCP carries out basic assessments in order to understand the patient's personal circumstances, symptom needs and the impact the patient's symptoms are having on their QoL. The HCP directs patients to the most applicable information and advice in the booklet. The HCP then conducts follow up contacts with the patient at 1 week (phone), 4 and 12 weeks (phone, text or email depending on patient preference) after receiving the intervention to offer encouragement and support. The comparator group is usual care in standard practice, which may vary between GP Practices.

2.6 Trial design

The TRIUMPH trial is a pragmatic, two-arm, cluster RCT where clusters are randomised at the level of the GP practices 1:1 between the intervention arm (standardised and manualised care intervention) and control group (usual care). Randomisation is minimised by centre (Bristol and Southampton), size of GP practice (number of registered patients at a practice) and level of deprivation (Index of Multiple Deprivation score based on the postcode of the GP practice). Power for the study is based on the primary outcome, which is to detect a clinical improvement in overall IPSS score of 2. IPSS is a patient-reported questionnaire, which will be completed at baseline, and 6 and 12 months after consent. Secondary outcomes measured through patient-reported questionnaires will be completed 6 and 12 months after consent. Primary-care medical records will be extracted at 12 months only. The senior statistician and senior health economist will be blinded throughout the trial. The junior trial statistician and health economist will conduct disaggregated analyses based on pre-specified analysis plans.

2.7 Trial start and end dates

Recruitment of the GP practices commenced in May 2018 and the first patient was recruited on 31th July 2018. The internal four-month pilot phase of recruitment was completed on 10th November 2018, while recruitment for the main trial ended at the start of August 2019. The 12-month follow up period ends August 2020 with the study closing in May 2021.

Section 3: Economic Approach

3.1 Aims of economic evaluation

The aim of the economic evaluation is to answer the following research question: "What is the within-trial cost-effectiveness of a manualised and standardised non-pharmacological intervention to treat men presenting in primary care with LUTS compared to usual care?"

3.2 Objective of the economic evaluation

The primary objective of the economic evaluation is to estimate the within-trial cost-effectiveness at 12-month follow up of a manualised and standardised non-pharmacological intervention versus usual care for patients experiencing bothersome LUTS.

3.3 Overview of economic analysis

Cost-effectiveness will be assessed using individual patient-level data from the TRIUMPH study. The Net Benefit (NB) framework will be used to assess cost-effectiveness over a range of values for the QALY including the UK's cost-effectiveness threshold (£20,000-£30,000 per QALY). In order to calculate a robust estimate of the expected NB, between group differences in costs and QALYs will be evaluated using appropriate regression techniques (e.g. multilevel modelling). Uncertainty in the results will be addressed using cost-effectiveness acceptability curves and sensitivity analyses. A secondary analysis will examine the between group difference in costs and IPSS score. If neither arm is dominant (i.e. both cheaper and more effective), then an incremental cost-effectiveness ratio (ICER) will be calculated in relation to the IPSS score.

3.4 Jurisdiction

The trial will be conducted in the UK where the health system is publicly funded and is free at the point of access.

3.5 Perspectives

All economic analyses will be conducted from the NHS perspective.

3.6 Time horizon

All analyses will compare costs and outcomes over the trial time horizon which will be from baseline to 12 months after patient consent.

Section 4: Economic Data Collection and Management

4.1 Statistical software use for health economic analysis

Stata version 16.1 or higher will be used for all health economic analyses.

4.2 Identification of resources

Relevant NHS resources identified as important include: (1) resources used for the training and delivery of the TRIUMPH intervention; and (2) Primary and secondary health care use. Primary health care includes consultations with key healthcare professionals (e.g. GP, Nurse and Healthcare Assistant). Primary care prescriptions include all LUTS-related medication. Secondary care use includes LUTS-related outpatient, day case, inpatient and accident and emergency (A&E) visits.

4.3 Measurement of resource use data

Intervention training and delivery costs

Resource use relating to training staff to deliver the intervention and ongoing support for staff delivering the intervention in the form of HCP teleconferences will be recorded by the research team. Data will include: type of staff, duration of training and travel expenses. Intervention delivery resources include resources which are standardised across patients (e.g. one intervention booklet per patient, an in-person consultation at week 0 and a phone consultation at week 1) and those which vary between patients (e.g. type of HCP, time to deliver consultations at week 0, 1, 4 and 12). HCPs will be asked to record this information at the end of each patient consultation in a case report form (CRF). In addition, in the week 4 and 12 CRFs, HCPs will be asked to record mode of delivery (phone, text, email).

Primary and secondary health care use

Health care resource use is being captured for: (1) all types of primary care consultations; (2) LUTS related prescribed medication; and (3) LUTS-related secondary care activity (e.g. outpatient, day case, inpatient and A&E visits). Information on primary care consultations and LUTS-related medications will be extracted from GP electronic medical records (EMRs). Secondary care LUTS related health care use will be obtained from self-completed questionnaires, administered either electronically or via a postal questionnaire. If deemed necessary, this information will be supplemented by information received by GP practices from hospitals (e.g. secondary care letters).

4.4 Valuation of resource use data

All primary and community healthcare resource use identified and measured will be valued in monetary terms in 2018/19 costs using the latest Unit Cost series by the Personal Social Services Research Unit (PSSRU) (6). Secondary healthcare resource use will be valued using NHS costs from the 2018/19 National Cost Collection (7). Prescribed medications will be assigned a unit cost from the British National Formulary (BNF) (8) or Prescription Cost Analysis (9); When a unit cost is not available for the year of analysis, it will be inflated to current prices using the NHS cost inflation index (NHSCII) as published in the Unit Cost series (6).

4.5 Identification of outcomes

The primary economic outcome measure will be Quality Adjusted Life Years (QALYs) derived from utility scores, obtained using the EQ-5D-5L quality of life instrument. The primary outcome from the clinical effectiveness evaluation, the IPSS, will be reported as a secondary outcome in the economic evaluation.

4.6 Measurement of outcomes

Outcomes will be collected at baseline, 6- and 12- months post consent, using a participant self-completed questionnaire. At baseline the questionnaire was administered via post, at 6- and 12-month follow up it could be completed online or via post.

4.7 Valuations of outcomes

Patients' EQ-5D-5L profiles will be mapped to the EQ-5D-3L valuation set using a validated mapping function by van Hout et al. (10) as recommended by National Institute for Health and Care Excellence (NICE). The valuation set enables a utility score to be calculated for each patient based on published UK population utility values. The area-under-the-curve approach will be used to transform the utility scores into QALYs for the 12-month time horizon. IPSS scores will be reported in their natural units (not monetised).

Section 5: Economic Data Analysis

5.1 Analysis population

All patients who did not withdraw their consent will be analysed according to the randomised allocation of their GP practice.

5.2 Timing of analyses

The final analysis will be conducted at the end of the trial, which will be 12 months post consent.

5.3 Discount rates for costs and benefits

As costs and benefits will not be assessed beyond 12 months post consent discounting will not be required.

5.4 Cost-effectiveness threshold(s)

Adjusted mean costs and QALYs associated with each comparator group will be combined through the NB framework. Cost-effectiveness will be evaluated using the NB framework over a range of values for the QALY, including the UK NICE recommended cost-effectiveness thresholds of £20,000-30,000 per QALY.

5.9 Data cleaning for analysis

The EMR will come from two different GP systems: EMIS and SystmOne. A SOP will be created to ensure that the final analysis dataset will be comparable across the two GP systems.

5.10 Missing data

Missing data will be handled depending upon the prevalence and likely cause of the missingness. The mechanism of missingness will be assessed. For example, if the data is believed to be missing at random (MAR), then multiple imputation methods may be used.

5.7 Analysis of resource use and costs

Mean resource use will be estimated and presented by trial arm for each resource use category (e.g. outpatient visits, medication use, etc.). Standard deviations (SD) and the number of patients included in each category by arm will also be presented. Appropriate regression techniques will be used to estimate adjusted mean costs and the difference in adjusted mean costs (and their associated 95% confidence intervals) between the trial arms. In order to take into account the cluster design nature of

the trial, multilevel modelling (MLM) will be used (i.e. to account for the correlation between patients from the same cluster- GP practice) (11-13). The MLM will adjust for the prespecified covariates used in the minimisation process (e.g. centre, practice size, area-level deprivation). In addition, type of GP system for EMRs will also be controlled for in the analysis. The multiple levels of the model include the individual patients (level 1) and the GP practices (level 2). Model choice for the MLM will be guided by examination of the residuals from the fixed and random parts. Alternative methods of analysis will be considered if the assumptions of the model are not be met. If costs are not normally distributed, they may need to be modelled with a gamma distribution through multilevel mixed-effects generalised linear modelling.

5.8 Analysis of outcomes

The primary economic outcome in the economic evaluation is Quality-Adjusted Life Years (QALYs). QALYs for each patient over the 12-month period will be calculated from the utility values using the area under the curve approach. Appropriate regression techniques such as MLM will be used to estimate adjusted mean QALYs and the difference in adjusted mean QALYs (and their associated 95% confidence intervals) between the trial arms taking into account the cluster design of the study (11-13). The MLM will adjust for the prespecified covariates used in the minimisation process (e.g. centre, practice size, area-level deprivation) and baseline utility (14). The multiple levels of the model include the individual patients (level 1) and the GP practices (level 2). The secondary outcome analysis will draw on the between group difference in mean IPSS score reported 12 months post consent as described in the SAP.

5.11 Analysis of cost-effectiveness

If neither arm is dominant (i.e. less expensive and more effective), incremental cost-effectiveness ratios (ICERs) will be created using the outputs from the appropriate regression. These outputs will also be used to estimate the incremental net monetary benefit (INMB) statistic at the standard NICE willingness to pay thresholds of both £20,000 and £30,000 per QALY. A secondary analysis will examine mean differences in IPSS score with mean differences in costs. If neither the intervention or usual care group is dominant (e.g. less expensive and more effective) then an ICER will be calculated, reporting the incremental cost per unit change in IPSS score.

5.12 Sampling uncertainty

Uncertainty will be addressed using cost-effectiveness acceptability curves for a range of willingness-to-pay thresholds. This assesses the probability of the intervention being the cost-effective option at a range of willingness-to-pay thresholds.

5.13 Subgroup analyses/Analysis of heterogeneity

An analysis will be performed in which patients who completed follow-up from 11th March 2020 (where 11th March 2020 refers to the date when the World Health Organisation declared the COVID-19 outbreak as a pandemic) will be compared to those who completed follow-up before this data.

5.14 Sensitivity Analyses

Uncertainty in the methodological choices made for the present economic evaluation will be assessed through a number of sensitivity analyses. This will involve making plausible changes to key methodological assumptions in order to understand how changes in the methodological assumption impacts of the cost-effectiveness result. Examples include:

- Inclusion/ exclusion of training and ongoing support costs
- Assuming intervention visits are/are not logged in the GP records
- Assuming all consultations had the same unit cost per healthcare professional type (regardless of mode of delivery)
- If applicable, different approaches to the handling of missing data

Section 6: Reporting/Publishing

6.1 Reporting standards

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines will be followed when reporting the health economic evaluation, in a format appropriate to stakeholders and policy makers.

6.2 Reporting deviations from the HEAP

Any deviation from HEAP will be documented and justified in the final published report.

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